

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

Claims 1-40 (Canceled).

41. (Presently Amended) A computer system for determining ~~biological pathways involved in the action of a drug in~~ a representation of measured drug response of a cell type to a drug in terms of one or more biological pathway responses, said computer system comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising the steps of:

(a) receiving a drug response of said drug in said cell type, said drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of drug exposure;

(b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in said cell type;

(c) forming a model drug response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of a function of the difference between said drug response and said model drug response; and

(e) minimizing said determined value of said function by varying the scaling transformations of said one or more biological pathway responses to obtain ~~best~~ scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said ~~best~~ scaling transformations ~~represents the biological pathways involved in the action of~~ a representation of said measured drug response of said drug in said cell type to said drug.

42. (Previously Presented) The computer system of claim 41 wherein said steps of receiving comprise making said drug response and said biological pathway responses available in said memory.

43. (Previously Presented) The computer system of claim 41 wherein said forming a model drug response comprises adding said one or more biological pathway responses.

44. (Previously Presented) The computer system of claim 41 wherein said function comprises a sum of squares of the differences of said drug response and said model drug response at said levels of drug exposure, said model drug response being provided at said levels of drug exposure by transforming by said scaling transformations said levels of drug exposure to corresponding levels of perturbations to each of said biological pathways and by interpolating said biological pathway responses to said corresponding levels of perturbations.

Claims 45-47 (Canceled).

48. (Previously Presented) The computer system of claim 41 wherein the method performed by said processor further comprises the steps of:

- (f) determining an expected probability distribution of minimized determined values of said function, and
- (g) assessing the statistical significance of the minimized determined value of said function in view of the expected probability distribution of minimized determined values of said function.

49. (Presently Amended) The computer system of claim 48 wherein the expected probability distribution of minimized determined values of said function is determined by:

- (i) randomizing the drug response with respect to the plurality of levels of drug exposure or randomizing the model drug response by randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;
- (ii) determining a theoretical minimum value of the function by a method comprising:

determining best scaling transformations of the one or more randomized biological pathway responses which minimize the function of the difference between the drug response and the randomized model

drug response, if the one or more biological pathway responses are randomized, or

determining best scaling transformations of the one or more biological pathway responses which minimize the function of the difference

between the randomized drug response and the model drug response, if the drug response is randomized; and

- (iii) repeating steps (i) through (ii) to determine a plurality of theoretical minimum values,

wherein said plurality of minimum values forms said expected probability distribution of minimized values.

50. (Presently Amended) The computer system of claim 41 wherein the method performed by the processor further comprises a step of verifying that said representation of said drug response ~~biological pathways are biological pathways involved in the action~~ is a representation of said drug response of said drug in said cell type to said drug by a method comprising selecting a model response that behaves most similarly to a combined drug-perturbation response, said combined drug perturbation response being provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of said cell type exposed simultaneously to one or more levels of said exposure to said drug and to one or more levels of perturbations in said one or more biological pathways,

wherein the model drug response is selected from the group consisting of:

- (i) a first model drug response comprising the combination of one or more biological pathway responses subject to the best scaling transformations evaluated at one or more first sums, each first sum being the sum of one of said one or more levels of drug exposure subject to said scaling transformations and one of said one or more levels of perturbations to said biological pathways.
- (ii) a second model drug response comprising one or more second sums, each second sum being the sum of said drug response evaluated at one of said one or more levels of drug exposure and said combination of said one or more biological pathway responses subject to the best scaling transformations evaluated at one of said one or more levels of perturbations to said biological pathways,

wherein said ~~biological pathways are~~ representation is verified as biological pathways actually involved in the action of said drug in as a representation of said drug response of said cell type to said drug if the first model response is selected.

51. (Presently Amended) The computer system of claim 41 wherein the method performed by the processor further comprises a step of assigning a cellular constituent present in said drug response to the one of said one or more biological pathways in which the biological pathway response of the cellular constituent subject to its best scaling transformation has the greatest correlation with the drug response of the cellular constituent.

52. (Previously Presented) The computer system of claim 41 wherein said scaling transformations comprise transformations of said levels of drug exposure to corresponding levels of said perturbations to said biological pathways.

53. (Previously Presented) The computer system of claim 52 wherein said transformations of said levels of drug exposure are by linear mapping.

54. (Previously Presented) The computer system of claim 41 wherein said one or more programs further cause said processor to interpolate the quantitative measurements of cellular constituents of the biological pathway in said cell of said cell type at a plurality of levels of perturbation so that the one or more biological pathway responses are interpolated.

55. (Previously Presented) The computer system of claim 54 wherein the interpolating comprises approximation by a sum of spline functions.

56. (Previously Presented) The computer system of claim 54 wherein the interpolating comprises approximation by a Hill function.

57. (Previously Presented) The computer system of claim 41 wherein the one or more biological pathways in the cell type are those biological pathways likely to be involved in the action of the drug in the cell type.

58. (Previously Presented) The computer system of claim 41 wherein the one or more biological pathways are selected from a compendium of biological pathways present in the cell type.

59. (Previously Presented) The computer system of claim 41 wherein the cell type is substantially isogeneic to *Saccharomyces cerevisiae*.

60. (Previously Presented) The computer system of claim 41 wherein the cellular constituents comprise abundances of a plurality of RNA species present in the cell type.

61. (Previously Presented) The computer system of claim 60 wherein the abundances of the plurality of RNA species are measured by a method comprising contacting a gene transcript array with RNA from a cell of the cell type, or with cDNA derived therefrom, wherein a gene transcript array comprises a surface with attached nucleic acids or nucleic acid mimics, said nucleic acids or nucleic acid mimics being capable of hybridizing with said plurality of RNA species or with cDNA species derived therefrom.

62. (Previously Presented) The computer system of claim 61 wherein the quantitative measurements of cellular constituents in step (a) are provided by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is exposed to said drug, and (ii) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is not exposed to said drug, and

wherein said quantitative measurements of cellular constituents in step (b) are provided by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is exposed to said perturbation to said biological pathway, and (ii) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is not exposed to said perturbation to said biological pathway.

63. (Previously Presented) The computer system of claim 41 wherein the cellular constituents comprise abundances of a plurality of protein species present in the cell type.

64. (Previously Presented) The computer system of claim 63 wherein the abundances of the plurality of protein species are measured by a method comprising contacting an antibody array with proteins from a cell of the cell type,

wherein the antibody array comprises a surface with attached antibodies that are capable of binding with the plurality of protein species.

65. (Previously Presented) The computer system of claim 63 wherein the abundances of the plurality of protein species are measured by a method comprising performing two-dimensional electrophoresis of proteins from a cell of the cell type.

66. (Previously Presented) The computer system of claim 41 wherein the cellular constituent comprise activities of a plurality of protein species present in the cell type.

67. (Previously Presented) The computer system of claim 41 wherein the one or more biological pathways in the cell type comprise biological pathways originating at one or more specific cellular constituents, and wherein the perturbations to the biological pathways are performed by a method comprising modifying the one or more specific cellular constituents.

68. (Previously Presented) The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising causing expression of the one or more specific cellular constituents under the control of a controllable expression system.

69. (Previously Presented) The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising controllable transfection of genes expressing the one or more specific cellular constituents.

70. (Previously Presented) The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing abundances of RNA species encoding the one or more specific cellular constituents in a cell of the cell type.

71. (Previously Presented) The computer system of claim 70 wherein the method of controllable decreasing abundances of RNA species comprises exposing a cell of the cell type to ribozymes targeted to cleave the RNA species.

72. (Previously Presented) The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing the rate of translation of RNA species encoding the one or more specific cellular constituents in a cell of the cell type.

73. (Previously Presented) The computer system of claim 72 wherein the method of controllably decreasing the rate of translation of RNA species comprises exposing a cell of

the cell type to antisense nucleic acids or antisense nucleic acid mimics that hybridize to the RNA species or to DNA encoding the RNA species.

74. (Previously Presented) The computer system of claim 67 wherein the one or more specific cellular constituents are abundances of protein species or activities of protein species, and wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing the abundances in a cell of the cell type.

75. (Previously Presented) The computer system of claim 74 wherein the method of controllably decreasing the abundances comprises causing expression in a cell of the cell type of the one or more protein species as fusion proteins comprising the protein species and a degron, wherein the degron is controllable to increase the rate of degradation of the protein species.

77. (Previously Presented) The computer system of claim 67 wherein the one or more specific cellular constituents are activities of protein species, and wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing the activities in a cell of the cell type.

78. (Previously Presented) The computer system of claim 77 wherein the method of controllably decreasing the activities comprises exposing a cell of the cell type to drugs which directly and specifically inhibit the activities of the protein species.

79. (Previously Presented) The computer system of claim 77 wherein the method of controllably decreasing the activities comprises exposing a cell of the cell type to dominant negative mutant protein species, wherein the dominant negative mutant protein species are proteins inhibiting said activities.

Claims 80-82 (Canceled).

83. (Presently Amended) A computer system for determining ~~biological pathways involved in the action of a drug in~~ a representation of measured drug response of a cell type to a drug in terms of one or more biological pathway responses, comprising
a process, and
a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method that comprises determining the ~~best~~ scaling transformation of one or more biological pathway responses which minimize the value of a function of the difference between a provided drug response and a model drug response, wherein:

- (a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in said cell type;
- (b) said provided drug response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said drug; and
- (c) said model drug response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said ~~best~~ scaling transformations ~~represents the biological pathways involved in the action~~ is a representation of said measured drug response of said drug in said cell type to said drug.

84. (Presently Amended) The computer system of claim 83 wherein said computer system assigns a statistical significance to the combination of said one or more biological pathway responses subject to said ~~best~~ scaling transformations, wherein the statistical significance is assigned by a method comprising:

- (a) obtaining an expected probability distribution of minimized values of the function; and
- (b) assessing statistical significance of an actual minimized value of the function in view of the expected probability distribution, wherein the actual minimized value of the function is determined from the provided drug response and the model drug response.

85. (Presently Amended) The computer system of claim 84 wherein the expected probability distribution is obtained by a method comprising:

- (a) randomizing the drug response with respect to the plurality of levels of drug exposure, or, randomizing the model drug response by a method comprising randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;
- (b) determining a theoretical minimum value of the function by a method comprising:
 - determining ~~best~~ scaling transformations of the one or more randomized biological pathway responses which minimize the function of the difference between the drug response and the randomized model drug response, if the one or more biological pathway responses are randomized, or
 - determining ~~best~~ scaling transformations of the one or more biological pathway responses which minimize the function of the difference between the randomized drug response and the model drug response, if the drug response is randomized; and
- (c) repeating steps (a) through (b), so that a plurality of theoretical minimum values is thereby determined,

wherein the plurality of theoretical minimum values forms the expected probability distribution.

86. (Presently Amended) A computer system for determining ~~biological pathways involved in the effect of an environmental change upon~~ a representation of measured environmental response of a cell type to an environmental change in terms of one or more biological pathway responses, said computer system comprising:

- a processor, and
- a memory coupled to said processor and encoding one or more programs,
- a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method that comprises determining the ~~best~~ scaling transformation of one or more biological pathway responses which minimize the value of an objective function of the difference between a received environmental response and a model environmental response, wherein:

- (a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in effect of said environmental change on said cell;
- (b) said received environmental response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said environmental change; and
- (c) said model environmental response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations ~~represents the biological pathways involved in the effect of said environmental change upon~~ is a representation of said measured environmental response of said cell type to said environmental change.

87. (Presently Amended) A computer system for determining ~~biological pathways involved in the effect of an environmental change upon~~ a representation of measured environmental response of a cell type to an environmental change in terms of one or more biological pathway responses, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

- (a) receiving an environmental response to said environmental change upon said cell type, said environmental response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of exposure to said environmental change;
- (b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a

plurality of levels of a perturbation to said biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in effect of said environmental change on said cell;

- (c) forming a model environmental response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;
- (d) determining the value of a function of the difference between said environmental response and said model environmental response; and
- (e) minimizing said determined value of said function by varying the scaling transformation of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations ~~represents the biological pathways involved in the effect of said environmental change upon~~ is a representation of said measured environmental response of said cell type to said environmental change.

88. (Canceled).